Biointerface Research in Applied Chemistry
Open-Access Journal (ISSN: 2069-5837)

Article
Volume 13, Issue 4, 2023, 316
https://doi.org/10.33263/BRIAC134.316

A Short Commentary of the Quality Control on Radix *Salvia miltiorrhiza* and its Application for COVID-19

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Scopus Author ID 56320935700
Received: 4.06.2022; Accepted: 5.06.2022; Published: 11.09.2022

Abstract: Radix *Salvia miltiorrhiza* (Danshen) is a Chinese herbal used in China to treat irregular menstruation, dysmenorrhea, insomnia, swelling liver, and angina pectoris. It also has various pharmacological activities, including anti-inflammation, anti-oxidation, anti-tumor, anti-atherogenesis, and anti-diabetes. However, traditional Chinese medicine (TCM), e.g., Danshen, lacks quality control. Pesticide residues and heavy metals are the most important problems, although Danshen may cure many diseases, even SARS-CoV-2 in a COVID-19 pandemic. Hence, the present short commentary discusses the background of Danshen, quality management, and its application to COVID-19.

Keywords: Radix *Salvia miltiorrhiza*; Danshen; quality control; COVID-19.

1. Introduction

Radix *Salvia miltiorrhiza*, also known as Danshen in China, was used in traditional Chinese medicine (TCM) a long time ago [1]. This belongs to the Lamiaceae family. Its surface is brick red and has lots of wrinkles.

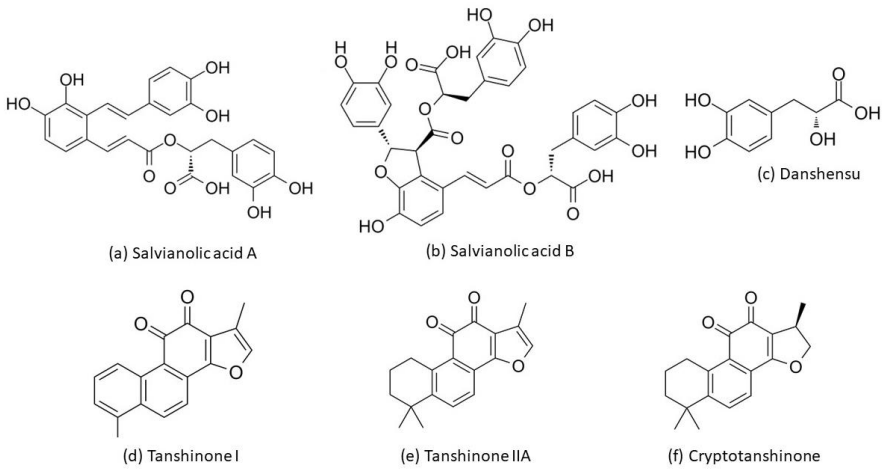

Figure 1. Chemical structures of (**a**) Salvianolic acid A; (**b**) Salvianolic acid B; (**c**) Danshensu; (**d**) Tanshinone I; (**e**) Tanshinone IIA; (**f**) Cryptotanshinone.

The odor is faint and slightly bitter-astringent in taste. Based on the TCM theory, the functions of Danshen are to promote blood circulation, remove blood stasis, clear heat, and claim nerves for the treatment of irregular menstruation, dysmenorrhea, insomnia, swelling

liver, and angina pectoris [2]. It consisted of 201 compounds, including lipophilic diterpenoids and water-soluble phenolic acids [3]. The major bioactive components were (a) Salvianolic acid A, (b) Salvianolic acid B, (c) Danshensu, (d) Tanshinone I, (e) Tanshinone IIA, and (f) Cryptotanshinone (Figure. 1), which possessed various pharmacological activities [4], such as anti-inflammation, and anti-oxidation, anti-tumor, anti-atherogenesis, and anti-diabetes (Table 1).

Table 1. Previous studies of pharmacological activities for Danshen.

	Lu TC *et al*. (2022) [5]	**Liu J *et al*. (2022) [6]**	**Cao Y *et al*. (2022) [7]**	**Tang Q *et al*. (2022) [8]**	**Zhang FX *et al*. (2022) [9]**
Objective	Targeting Oxidative Stress and Endothelial Dysfunction Using Tanshinone IIA for the Treatment of Tissue Inflammation and Fibrosis	*Salvia miltiorrhiza* Bge. (Danshen) in the Treating Non-alcoholic Fatty Liver Disease Based on the Regulator of Metabolic Targets	Danshensu Attenuated Epithelial-Mesenchymal Transformation and Chemoresistance of Colon Cancer Cells Induced by Platelets	A green and highly efficient method to deliver hydrophilic polyphenols of *Salvia miltiorrhiza* and Carthamus tinctorius for enhanced anti-atherosclerotic effect via metal-phenolic network	Dissection of the potential anti-diabetes mechanism of salvianolic acid B by metabolite profiling and network pharmacology
Function	Anti-inflammatory	Anti-oxidation	Anti-tumor	Anti-atherogenesis	Anti-diabetes
Result	Tan IIA suppresses tissue inflammation and fibrosis through signaling pathways such as PI3K/Akt/mTOR/eNOS, TGF-*β*1/Smad2/3, NF-*κ*B, JNK/SAPK (stress-activated protein kinase)/MAPK, and ERK/Nrf2 pathways.	Danshen in the management of NAFLD based on metabolic targets c-Jun N-terminal kinases (JNK), sterol regulatory element-binding protein-1c (SREBP-1c), and nuclear translocation carbohydrate response element-binding protein (ChREBP)	Danshensu diminishes the secretion of some biological factors in SW620 cells with direct contact, including interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), IL-1β, and vascular endothelial growth factor (VEGF) which are all involved in tumor cell EMT and chemoresistance	The four coordination polymers, salvianic acid A (SAA), salvianic acid B (SAB), protocatechuic aldehyde (PCA), and hydroxysafflor yellow A (HSYA) show remarkably enhancing anti-atherosclerotic effect compare with free drugs, which display potent antioxidant activity, good biocompatibility, and stability	Salvianolic acid B and its metabolites regulate ALB, PLG, ACE, CASP3, MMP9, MMP2, MTOR, etc, which are involved in the insulin signaling pathway, PI3K-Akt signaling pathway, HIF-1 signaling pathway, TNF signaling pathway
Significance	The therapeutic value of TanIIA in the alleviation of oxidative stress, inflammation, and fibrosis	A critical assessment of the preclinic, clinic model and the molecular mechanism in non-alcoholic fatty liver disease are developed	Danshensu is attenuated epithelial-mesenchymal transformation (EMT)-like characteristics and chemoresistance	Metal-phenolic network-based coordination polymer shows great potential for safe and efficient delivery of the hydrophilic polyphenols of *salvia miltiorrhiza*	Salvianolic acid B *in vivo* is systematically revealed, and its anti-diabetes mechanism for further pharmacological validations is predicted
Disease	Cardiovascular disorders	Non-alcoholic fatty liver disease	Colon cancer	Cardiovascular disease	Diabetes

1.1. Quality control.

However, pesticide residues and heavy metals are the most important standards to monitor the quality and safety of a traditional Chinese herb, e.g., Radix *Salvia miltiorrhiza* [10]. Guo N *et al*. reported that 2.4% of Dan-Shen Root exceeded the standard of pesticide residues and heavy metals [11]. Since the advent of an industrialization and urbanization era in China, soil pollution has become serious in the agriculture of Chinese herbs, such as chemical wastes and pesticides, including organochlorine and organophosphorus residues. These might transform into harmless materials and be difficult to self-decomposition, which accumulate within the human body affecting the central nervous system (CNS) (Table 2) [12].

The most common heavy metals are Arsenic, Cadmium, Lead, and Mercury, which influence the quality of soil minerals. These are hard to biodegradable, which increases the biological toxicity of Chinese herbs and danger to the human body [13, 14]. Based on Hong Kong Chinese Materia Medica Standard (Volume 9), the standard of pesticide residues and heavy metals in Chinese Pharmacopoeia are shown below (Table 3) [15].

Table 2. The limited contents of pesticide residues in Chinese Pharmacopoeia.

	Name of pesticide residues	**Testing Range**	**Contents (mg/kg)**
Organochlorine pesticide residues	Dichloro-diphenyl-trichloroethane (DDT)	Sum of p,p'-DDT, o,p'-DDT, p,p'-DDE and p,p'-TDE.	1.0
	Hexachlorocyclohexane (BHC)	Sum of α-, β- and δ-isomers	0.3

	Name of pesticide residues	Testing Range	Contents (mg/kg)
	Quintozene (PCNB)	Sum of quintozene, pentachloroaniline, and methyl pentachlorophenyl sulphide	1.0
	Hexachlorobenzene	Hexachlorobenzene	0.1
Organophosphorus pesticide residues	Dichlorvos	N/A	Checking out the content is Prohibited
	Methamidophos		
	Parathion-methyl		
	Phosphamidon		
	Ethion		
	Methidathion		
	Chlorpyriphos		

Table 3. The limitation contents of heavy metals in Chinese Pharmacopoeia.

Heavy metals	Contents (mg/kg)
Copper(Cu)	< 20
Lead (Pb)	< 5
Cadmium (Cd)	< 1
Arsenic (As)	< 2
Mercury (Hg)	< 0.2

1.2. COVID-19.

In the December of 2019, there was an outbreak of pneumonia with unknown etiology emerged in Wuhan of Hubei Province, China. This pneumonia outbreak was caused by the coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). World Health Organization (WHO) has termed this SARS-CoV-2 as coronavirus disease 2019 (COVID-19) [16, 17].

Traditional Chinese Medicine (TCM) has played a crucial role in stopping, preventing, and treating the COVID-19 pandemic, including Jinhua Qinggan granules, Lianhua Qingwen capsule, Qingfei Paidu decoction, Huashi Baidu formula, Xuanfei Baidu formula [18]. Single Chinese herbals such as curcumin [19] and astragalus [20] also have shown beneficial effects on the progression of inflammatory diseases because their numerous action mechanisms contain antiviral, anti-inflammatory, anticoagulant, antiplatelet, and cytoprotective that are used for the treatment of COVID-19.

Many single Chinese herbals are possible for combating COVID-19, e,g, Danshen. This may be one of the candidates, but its quality should be maintained, which influences the effectiveness of treatment for COVID-19. Thus, this short commentary is divided into two parts, including (i) Quality control of Danshen; and (ii) its application for COVID-19.

2. Methods

Nine electronic databases, including China National Knowledge Infrastructure (CNKI), WanFang Data, PubMed, Science Direct, Scopus, Web of Science, Springer Link, SciFinder, and Google Scholar, were searched from 2012 to 2022 within ten years and without language restrictions. The keywords searched such as "quality control + Danshen", “SARS-CoV-2 + Danshen”, “COVID-19”, “COVID-19 + Danshen” etc. All eligible studies are analyzed and summarized in the commentary.

3. Research Progress

3.1. Quality control of Danshen.

Establishing an applicable quality control method and evaluation system is crucial content to realize the standardization, modernization, and internationalization of TCM, e.g., Danshen [21]. According to the Chinese Pharmacopoeia, Gas chromatography-mass spectrometry (GC-MS) is the major instrument to determine pesticide residues; whilst Inductively coupled plasma mass spectrometry (ICP-MS) or optical emission spectrometry (ICP-OES) and Atomic absorption spectroscopy (AAS) is used to identify the heavy metals.

3.1.1. Gas chromatography-mass spectrometry (GC-MS).

GC-MS detects organochlorine pesticide residues by selective mass-to-charge ions. Ten organochlorine pesticides, including alpha, beta, gamma, and delta isomers of HCH, pp'-DDE, pp'-DDT, op'-DDT, pp'-DDT, PCNB, and HCB are determined simultaneously. Samples are pre-concentration, extracted with acetone, partitioned using petroleum ester with saturated sodium chloride aqueous solution, and clean-up with concentrated sulfuric acid before GC-MS analysis [22].

3.1.2. Inductively coupled plasma mass spectrometry (ICP-MS) or optical emission spectrometry (ICP-OES).

Heavy metals, including Arsenic, Cadmium, Lead, Mercury, and copper, are analyzed by ICP-MS or ICP-OES. Samples are acid digestion with H_2O_2 and HNO_3, HCl for microwave digestion, and dilution with milli-Q water before starting ICP-MS or ICP-OES determination [23].

3.1.3. Atomic absorption spectroscopy (AAS).

Similar to 3.1.2., samples are acid digestion to remove impurities and identify heavy metals [24, 25].

3.2. Danshen for COVID-19.

Growing evidence has shown that Danshen might be a possible Chinese herbal for treating SARS-CoV-2. Wang W *et al*. reported the bioactive component, Salvianolic acid C from Danshen, potently inhibited SARS-CoV-2 infection, which reduced the number of inflammatory cells, prevented damaging lung tissue structure, and decreased the expression levels of inflammatory cytokines, as well as deactivated TLR4 and hyperphosphorylation of the NF-κB p65. Danshensu was also an antiviral agent that affected the expression of angiotensinogen (AGT) and angiotensin-converting enzyme 2 (ACE2) on the mRNA to lower an inflammation response in the lung tissue [26].

Petitjean SJL *et al*. discovered the preclinical potential of *S. miltiorrhiza* extracts that interfered with the inflammatory response of blood mononuclear cells (PBMCs). It inhibited the pro-inflammatory cytokine release and interference with the activation of NFκB signaling, which blockage the binding between SARS-CoV-2 and cellular ACE2 receptors, reducing inflammation in the lung [27].

Niu W *et al*. also identified Danshan with the transcription factor (TF) that could bind to a gene promoter and modulate its expression. The microRNAs (miRNAs) suppressed the

gene expression by binding to the 3'-UTR of their mRNAs. These were the important regulators of gene expression to reduce the binding with ACE2 for SARS-CoV-2 infection, which decreased the chance of lung inflammation [28].

4. Discussion

Pesticide residues and heavy metals contamination are serious problems for Chinese herbals, especially at a higher threshold concentration level. The Chinese herbals also have at least one over-limit metal, according to Chinese Pharmacopoeia findings [29]. How do we maintain the quality of TCM? Can we remove or eliminate the pesticide residues and heavy metals from TCM?

He H *et al*. reported the effect of processing on the reduction of pesticide residues in TCM through the processing steps, including washing, steaming and drying, carbonizing, and boiling. The pesticide residues from TCM decreased by 41.2%-60.0% in washing and 27.1%-71.1% in carbonizing. The concentrations of tebuconazole and prochloraz reduced from 0.0002 to 0.0022 mg kg^{-1} in decoctions [30].

Xiao Q *et al*. also designed a novel genetically engineered fusion protein composed of metallothionein (MT), cellulose-binding module (CBM), and super folder GFP (sfGFP) to remove heavy metals from the water decoction of TCM. The sfGFP was used to detect the fusion protein through the process of expression and immobilization, and the cell lysates were mechanically mixed with cellulose (CBM) and metallothionein (MT) to create bio-sorbents for removing heavy metals without affecting its active ingredients [31].

Danshen is possible to treat SARS-CoV-2 in a COVID-19 pandemic, as discussed above. Benarba B *et al*. identified that 30 µg/ml of *Salvia miltiorrhiza* Bunge ethanolic extract caused 88% inhibition of SARS-CoV PLpro. Seven bioactive components from *Salvia miltiorrhiza* Bunge, including tanshinone IIA, tanshinone IIB, methyl tanshinonate, cryptotanshinone, tanshinone I, dihydrotanshinone I, and rosmariquinone were extracted with IC_{50} of 0.8 to 30 µM for inhibition. Cryptotanshinone was the most potent inhibitor of SARS-CoV PLpro with an IC_{50} of 0.8 ± 0.2 µM [32].

5. Conclusion

As the evidence mentioned, the quality control of Radix *Salvia miltiorrhiza* is based on the concentrations of pesticide residues and heavy metals detected in GC-MS, ICP-MS, ICP-OES, and AAS, respectively, according to the safety level in Chinese Pharmacopoeia. Additional processing steps include washing, steaming and drying, carbonizing, and boiling, as well as bio-sorbents that are effective in removing pesticide residues and heavy metals. Radix *Salvia miltiorrhiza* is also a TCM for treating SARS-CoV-2 in a COVID-19 pandemic. However, much more works need to be done for further development, such as safety assessments (e.g., dosage and formulation) in the human clinical study.

Funding

This research received no external funding.

Acknowledgments

None.

Conflicts of Interest

The authors declare no conflict of interest. Some contents are part of the Xinchen Lu from Bachelor of Science (Honours) in Chinese Medicinal Pharmacy (THEi), 2020.

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